

Traversing the Landscape Of Project BioShield

The U.S. government recently signed on to help Bavarian Nordic through the Valley of Death. There's a lot riding on this trip.

Their journey officially began in June, when the Department of Health and Human Services granted the drug developer a five-year, \$500 million contract for 20 million doses of Imvamune, an experimental smallpox vaccine. Options boosted that sum to a potential \$1.6 billion, depending on the company's ability to advance the new vaccine. Up to 60 million doses and the cost of clinical studies to expand the drug's reach to other patient populations would be covered by these options.

This joint venture was the first of many envisioned by the government, which for years has been urging developers to come up with an effective stockpile of remedies to defend the country against bioterrorism. Frustrated by the lack of progress under the original Project BioShield, Congress late last year created the Biomedical Advanced Research and Development Authority (BARDA) to manage that and other programs, including pandemic preparedness. The bill included a significant change of course for the program.

As it was originally set up, officials with the \$5.6 billion Project BioShield had to wait for product delivery before the government could pay for them. But with big biotech companies largely shunning a program viewed as high-risk with low potential returns, the smaller developers that were left repeatedly ran into problems.

Case in point: the same day the president signed the new bill, the government scrapped a billion-dollar contract for a vaccine from Vaxgen that had foundered in clinical trials.

Under BARDA, however, the government offered to sign new deals to fund research as products hit milestones along the approval path — money that would be a lifeline while companies traversed the Valley of Death.

Skeptics abound, however. They say Project BioShield is long on promises and short on performance. They also say past experience leaves little confidence that the agency will be able to turn things around in the new, revised Project BioShield.

But some hopeful drug developers say this new initiative has created some promising opportunities.

"I think they're moving in the right direction," offers Alan Wolfman, PhD, director of business development for Cleveland BioLabs. "As outsiders, of course, we always want them to move faster than they could."

"I've been encouraged with some of the short-term stuff I've seen," says Andrea Meyerhoff, MD, a principal of GexGroup and a former government official turned biodefense consultant. "There's a real commitment to transparency. They've held annual meetings, both last summer and this year, and that's a nice way to

get an overview. They're launching a Web site, which has been a long time coming and is good to see. There's a new attention to process, a lot of hiring and building up of their infrastructure."

But six years after the anthrax mail attacks, and three years since the original BioShield legislation was signed, she adds, "I don't like to say it, but it's still very early."

The Bavarian Nordic contract "was the first piece of good news" since the new legislation passed in December, says Brad Smith, PhD, a molecular biologist and senior associate at the Center for Biosecurity.



President Bush signs the Project BioShield Act in the Rose Garden, July 21, 2004.

of the University of Pittsburgh Medical Center. "That contract used some of the new authority, the most significant of which was the ability to have true milestones in a BioShield contract."

Because BioShield contracts pay the developer only upon delivery of the final product, the biotech company bears almost all of the risk while HHS faces very little. In addition, the advance-payment clause in the original BioShield legislation required repayment of any advance monies to the government if the product failed in development. Given these risks,

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says Smith, creating medicines and vaccines became unappealing to biotech developers.

The new BioShield milestone payments created by the PAHPA legislation do not have to be repaid. Under the new guidelines, the hope is the government can take less risk by funding drug research and development at several companies, Smith adds, gradually winnowing down the number of candidates as they progress down the pipeline. But since HHS has yet to issue a BARDA advanced development contract, he says, it's unclear if it will opt to fund multiple candidates. In the new scenario, the developer can gain 5 percent of the contract value at every milestone, up to 50 percent of the total. "That, I think, is an important new opportunity for the government and companies interested in this space," says Smith.

On the down side, though, Smith notes that government officials are taking typically between 8 to 11 months to review contracts, "and that's a very long time for a company to tread water."

BARDA has been busily adding staffers, he adds, but the next big step is bringing in an experienced chief to run the agency. "It seems to have been in a state of suspended animation for a while. There's concern that HHS is being very conservative in the way the drug development process is being approached. HHS only has \$5.6 billion, and Congress hasn't shown a willingness to provide more money."

Congress also has been slow to approve development funds, Smith adds. "We'll be lucky to get \$250 million in total for BARDA advanced development contracts in fiscal year 2008," he says. "That's a lot of money in health budget terms, but not in drug develop-

ment terms. We think the amount of funding isn't enough for a successful mission." If the government ends up with new tools to support the field while starving the program of cash, he says, "We'll be back to where we were a year ago, with many people concerned about where we're going."

GREAT IDEA, POOR EXECUTION

"This is a new endeavor for the biotech industry and HHS," says Smith, "to really build a partnership and figure out how to develop drugs together — something that hasn't happened yet."

Some people think it never will.

The big problem with Project BioShield is that HHS never implemented it the way lawmakers spelled out in the 2004 legislation, says Richard Hollis, CEO of Hollis-Eden Pharmaceuticals, in San Diego, which had counted on those advanced purchase contracts. If you had a viable market candidate that was within eight years of approval from the U.S. Food and Drug Administration, explains Hollis, the agency would guarantee the market by entering into an advance purchase contract to pay for the product upon FDA approval. Because the markets were never set, as specified in the legislation, the government never created the carrots meant to lure developers into the antibioterror field.

Hollis focused his company primarily on delivering a radiation countermeasure — Neumune — from 2003 to 2007. His talks with the government during that time, Hollis says, were punctuated with regular assurances of a coming supply contract. Delays followed.

HHS unilaterally cancelled its request for proposal. In March, Hollis was told the acute radiation syndrome therapy was "'not technically acceptable.' We've come to

believe that means 'not approved by the FDA.'" And that, he says emphatically, was not the law's intent.

Eden was forced to pink slip about a quarter of its workforce and rapidly shift away from Project BioShield toward development programs for two experimental therapies that had been steadily advancing while the company struggled to make its relationship with BioShield work.

Hollis isn't optimistic that channeling government funds into research and development will pay off for taxpayers or biotechs.

"Press releases note HHS will staff up BARDA with over 300 personnel, and drugs will be developed through grants," Hollis says. "To us, that's not a very viable commercial avenue to pursue."

"Six years after 9/11, we still don't know the absolute threats, the markets, and how the government will develop countermeasures," says Hollis, still clearly disappointed by the program's failure to meet its original promise.

"There is no Valley of Death in the private sector," says Hollis. "If a technology is promising, there's a market for it, and the approval path is clearly defined. Companies have no difficulty obtaining investor capital — even though typical drug development costs hundreds of millions of dollars, takes over a decade, and many promising compounds aren't approved. Pharmaceutical and biotech investors understand risk and reward. By changing the criteria for companies to be awarded an advance purchase contract, HHS has pushed the investors away from BioShield. They have created their own Valley of Death." **BH**

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